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# Effect of N-acetylcysteine in Indeterminate Acute Liver Failure

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## ABSTRACT

**Background:** Acute liver failure (ALF) is a rare syndrome, characterized by acute derangement of liver function and carries high mortality. Indeterminate ALF still forms a significant number of cases in India as well in the world. A prospective case-control study was carried with the aim to determine the effect of N-Acetylcysteine (NAC) on the survival of indeterminate ALF patients.

**Methods:** A total of 30 patients with a diagnosis of indeterminate ALF were included in the study. 14 patients received NAC infusion for 72hrs whereas 16 patients in control group received placebo. The parameters evaluated were demographic, clinical, biochemical, outcome and length of hospital stay.

**Results:** The two groups were comparable for the various baseline characteristics (demographic, clinical, biochemical etc.). A total of 18 of 30 (60%) patients died with ALF complications; 6 (42.8%) patients belonged to NAC group and 12 (75%) patients to Control group ( $P = 0.077$ ). The overall survival was not improved by NAC in indeterminate ALF. Use of NAC also did not reduce the duration of hospital stay of survived patients ( $P = 0.409$ ).

**Conclusion:** The overall survival was not improved by NAC in indeterminate ALF. NAC administration did not reduce the duration of hospital stay.

**Key Words:** Acute Liver Failure (ALF), Indeterminate ALF, Hepatic encephalopathy (HE), N-Acetylcysteine (NAC)

## INTRODUCTION

Acute liver failure (ALF) remains a clinical challenge and still accounts for high mortality, particularly when the cause remains unclear. ALF is a syndrome characterized by the development of hepatic encephalopathy (HE) together with signs of hepatocellular insufficiency, especially jaundice and coagulation disorders, in patients without previous liver disease.<sup>[1]</sup> It is a rare disease with 2000 to 3000 reported cases in the United States per year.<sup>[2]</sup> Reports from the developed world suggest an overall incidence of 1 - 8 cases per million people every year,<sup>[3]</sup> yet it accounts for up to 7% of all liver-related deaths<sup>[2]</sup> and is responsible for 6% of liver transplants.<sup>[4]</sup> However, spontaneous recovery is observed in up to 45% of ALF patients, and specific treatments for known etiologies can be effective.<sup>[5]</sup>

The term acute liver failure is used to describe the development of coagulopathy, usually with an international normalized ratio (INR) of greater than 1.5, and any degree of mental

alteration (encephalopathy) in a patient without preexisting cirrhosis and with an illness of less than 26 weeks duration.<sup>[6]</sup>

Etiology of ALF is heterogeneous and shows wide geographical variation. The most important step in the management of ALF is to identify the cause which helps in the execution of targeted therapies and antidotes, when available. The main etiological factor includes: viral, drugs including herbal and traditional medications, autoimmune, toxin and indeterminate.<sup>[7]</sup> Acetaminophen overdose is the most common cause of ALF in the United States and Europe, whereas viral hepatitis is more common in Asia and Africa, but numerous other causes have been reported, including drug-induced liver injury, viral hepatitis, ischemic liver injury, Wilson's disease, and acute presentation of autoimmune hepatitis.<sup>[8, 9]</sup> Viral hepatitis is the commonest cause of ALF world-wide and in the Indian subcontinent alone it accounts for 90% of cases.<sup>[10]</sup>

Causation cannot be established in many cases; such seronegative or indeterminate liver failures happens worldwide,

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and are associated with especially poor survival with medical therapy alone, and frequently need emergency transplantation.<sup>[11,12]</sup> A significant minority of ALF cases, however, cannot be linked to a clear cause. 18% to 20% of ALF cases in industrialized countries have an unknown etiology.<sup>[13]</sup> They usually present with an acute or subacute ALF phenotype.<sup>[14]</sup> A proportion of these patients may have taken drugs or xenobiotics, which they do not (or cannot) recall. Others provide a history compatible with a viral phenotype, although no specific viral etiological agent can be identified.<sup>[15]</sup> Some subsequently present with immune-mediated features, suggesting that the original disease may have been autoimmune in nature. In some of these groups, as well as in those of a known etiology, the potential for paracetamol-induced co-toxicity may be raised by the presence of paracetamol adducts.<sup>[16]</sup> Equally, studies have suggested that some cases of presumed seronegative etiologies may have HEV infection, and appropriate tests regarding sensitivity and specificity should always be undertaken.<sup>[17]</sup>

Mortality related to ALF can be attributed to three complications in particular: cerebral edema, multiorgan dysfunction syndrome, and sepsis. Liver has the unique ability to regenerate after acute, self-limiting injury. The overall management strategy starts with the identification of cause and an initial assessment of prognosis. Although many people recover with supportive treatment; Orthotopic liver transplantation (OLT) remains the only definitive therapy for patients who are unable to achieve sufficient hepatocyte regeneration on supportive treatment. OLT has made a significant impact on the survival of patients with ALF.<sup>[18, 19]</sup> Therefore better cost-effective alternatives are needed in locations where facility is not available. N-Acetylcysteine (NAC) has a well-established role in paracetamol-induced ALF<sup>[20]</sup> although it is now also recommended in selected cases of non-paracetamol ALF<sup>[21-23]</sup> because of its multiple mechanisms of action.

NAC is a thiol-containing agent that scavenges free oxygen radicals and replenishes cellular mitochondrial and cytosolic glutathione.<sup>[24, 25]</sup> Its anti-inflammatory, antioxidant, inotropic, and vasodilating effect has been proved from various trials.<sup>[26, 27]</sup> NAC may benefit patients either by improving systemic hemodynamics and tissue oxygen delivery<sup>[28]</sup> or via other mechanisms.<sup>[29]</sup> Role of NAC in indeterminate ALF has not been studied in controlled trials. In this prospective study, we aimed to determine the role of NAC on mortality in indeterminate ALF and also to evaluate the safety and efficacy of NAC and its impact on the duration of hospital stay at a tertiary care centre in Kashmir (North India).

## MATERIALS AND METHODS

It was a single centre prospective study of adult patients with indeterminate ALF. This study was carried out in the De-

partment of Gastroenterology of Sher-i-Kashmir Institute of Medical Science (SKIMS), Soura, J&K. The study was approved by the institutional ethical committee (SKIMS). Informed consent was obtained from all the recruited subjects.

## Study subjects

Total of 30 patients with diagnoses of indeterminate ALF who fulfilled eligibility criteria were recruited in the study. This study was conducted over a period of three years from April 2011 to April 2014. Information regarding various demographic characteristics was taken through well-structured questionnaires from all subjects. Besides a detailed history, physical examination and biochemical workup which included baseline investigations, liver function test (LFT), coagulogram of subjects were carried out.

**Eligibility criteria:** Inclusion criteria include patients having age >18 years and ALF was defined as biochemical evidence of acute liver injury with INR  $\geq 1.5$  and any degree of encephalopathy caused by the illness of duration <26 weeks in a patient with no prior known liver disease and with no established etiology of ALF.

Exclusion criteria include i) Viral-ALF, ii) Drug-induced ALF, iii) Autoimmune ALF, iv) Acute on chronic liver failure, v) ALF during pregnancy, vi) Hepatic shock.

## Detailed study design

After ALF was diagnosed, a detailed history was taken for any hepatotoxic drug intake, including homeopathic, herbal medications and intravenous drug abuse. Indeterminate cause was diagnosed in a patient with: (i) clinical and biochemical features of FHF, (ii) absence of acute viral markers of known hepatitis viruses (A-E), (iii) no exposure to drugs, hepatotoxins, systemic infections, biliary obstruction/infection and metabolic liver diseases. Blood samples of all the patients were taken for the etiological diagnoses, which included hepatitis B surface antigen (HBsAg), hepatitis B core IgM (HBc-IgM), hepatitis A virus IgM (HAV-IgM), and hepatitis E virus IgM (HEV-IgM), hepatitis D virus (IgG and IgM anti-HDV), anti HCV (hepatitis C virus), ANA (anti nuclear antibody), ASMA (anti smooth muscle antibody), Wilson profile (serum ceruloplasmin, serum copper) and iron profile. HSV (herpes simplex virus), CMV (cytomegalovirus) and EBV (Epstein barr virus) serology were done if non hepatotropic viruses were suspected as a cause of ALF. Imaging was obtained to rule out biliary processes, hepatic vascular abnormalities, and intrahepatic lesions. All the ethical considerations were taken care of during the study. Subjects were then randomized by simple random method into two groups.

**NAC Group:** 14 indeterminate ALF patients who fulfilled the eligibility criteria were treated with intravenous NAC for a duration of 72 hours.

**Control Group:** 16 indeterminate ALF patients received 5% dextrose (placebo) infusion for 72 hours.

### Study medication

After informed written consent was obtained from next of kin, the patients in NAC group were administered intravenous NAC with an initial loading dose of 150 mg/kg over 1 hour, followed by 12.5mg/kg/hr for 4 hours and then continuous infusion of 6.25mg/kg/hr for remaining 67 hours. Patients in Control group were given 5% dextrose infusion (placebo) for 72 hours. All the ethical considerations were taken care of during the study. Patients were given the option of liver transplant (to be done at the hospital with transplantation facility) at various stages of a study when indicated. No patient underwent OLT.

### Supportive treatment

All patients were managed with the standard supportive care treatment.<sup>[30]</sup> The patients received treatment of and prevention for the complications of ALF. The treatment mainly involved continuous intravenous dextrose to prevent hypoglycemia; proton pump inhibitors for stress-related ulcers and lactulose enema. With the development of advanced HE, intensive care management, fluid and electrolyte balance, midazolam sedation and mannitol infusion in case of raised intracranial pressure. Intracranial hypertension was diagnosed clinically in the presence of clinical signs such as abnormal pupillary reflexes, hypertonia or decerebrate posturing. Fresh frozen plasma and vitamin K was given in only those patients who had a spontaneous bleed. Blood and urine cultures were obtained in suspected cases of sepsis, which were then treated as per sensitivity. Renal impairment was defined as a serum creatinine level of more than 1.5 mg/dl. Response to treatment was monitored clinically (Grade of encephalopathy) and biochemically (bilirubin, PT, INR, etc.). In addition, morbidity and mortality were also assessed. Patients were followed till discharge or death in hospital.

### Statistical analyses

Frequency distribution was assessed in terms of means  $\pm$  SD for quantitative variables and number (percentages) for categorical variables. In univariate analysis, the categorical variables were compared by using  $\chi^2$  test or Fisher exact test where appropriate. For continuous variables, the independent sample t-test was used.  $P$  values  $<0.05$  was considered statistically significant. All the analyses were performed by the Statistical Package for Social Sciences (SPSS, Chicago, IL, USA, version 21.0).

## RESULTS

There were 30 patients of indeterminate ALF in total. There were 14 patients in the NAC group and 16 patients in Con-

trol group. Table 1 shows the distribution of baseline characteristics (both categorical and continuous) of two groups of indeterminate ALF. The mean age in NAC group was  $35.5 \pm 16.2$  years and in Control group was  $33.9 \pm 20.2$  years ( $P = 0.814$ ). Majority of the patients were females (56.7%) and they were equally distributed between two groups. Coma grade at the time of admission showed that majority of patients (60%) had grade III and IV encephalopathy. The patients in both groups were comparable for the different grade of encephalopathy ( $P = 0.305$ ). The two treatment groups did not differ significantly with respect to fever, vomiting, creatinine, Model For End-Stage Liver Disease (MELD) Score, interval between jaundice and encephalopathy, mean grade of coma and biochemical measures of liver injury (INR, bilirubin, AST, ALT, and albumin).

The mean number of days of admission in hospital of survived patients in NAC group was  $9.4 \pm 4.2$  versus  $11.6 \pm 4.1$  in Controls. The difference was not significant ( $P = 0.409$ ) (Table 2). A total of 18 of 30 (60%) patients died with ALF complications; 6 (42.8%) patients belonged to NAC group and 12 (75%) patients to Control group (Chi Sq. = 3.118;  $P = 0.077$ ).

More patients (57.2%) survived in NAC group than in the Control group (25%) but the difference was not statistically significant (Table 3).

Logistic regression analysis was performed in order to study the role of independent risk factors on mortality in indeterminate ALF patients. In the study age  $>50$  years, III-IV grade of encephalopathy, renal impairment, MELD score  $>30$  and bilirubin  $>20$ mg/dl were the independent prognostic factors determining mortality.

## DISCUSSION

Acute liver failure (ALF) is a dynamic clinical condition manifested by an abrupt onset of a liver-based coagulopathy and biochemical evidence of hepatocellular injury resulting from rapid deterioration in liver cell function.<sup>[31]</sup> The correct determination of etiology in ALF is vital for both therapeutic and prognostic considerations and the use of antidotes depends on the identification of the causative process. OLT has now become an established treatment option in patients with ALF. Due to a lack of OLT facility, NAC has emerged as a beneficial treatment for non-paracetamol ALF.<sup>[21-23]</sup> Role of NAC in Viral-ALF has not been studied in controlled trials. So the prospective study was carried out to determine the role of NAC on mortality in indeterminate ALF and also to evaluate the safety and efficacy of NAC and its impact on the duration of hospital stay at a tertiary care centre in Kashmir (North India).

In our study there were 30 patients of indeterminate ALF, which constituted around 35% of cases of 84 ALF patients,



an endemic zone for HEV.<sup>[32]</sup> Similar percentage of indeterminate cause of ALF was shown by Khuroo MS, et al <sup>[33]</sup> while western studies reported less percentage<sup>7</sup> and other studies even reported a higher percentage.<sup>[34]</sup> There were 14 patients in the NAC group and 16 patients in Control group.

In this prospective case-control trial, more patients (57.2%) survived in NAC group than in the Control group (25%) but no significant improvement in the survival of patients who were treated with NAC was seen ( $P = 0.077$ ). Furthermore, the use of NAC was not associated with a shorter length of hospital stay in survived patients ( $P = 0.409$ ).

The previous study by us showed that NAC improved the overall survival in non-acetaminophen induced ALF with a more favourable effect on drug-induced ALF.<sup>[21]</sup> Other studies also reported NAC improved transplant-free survival in early stage non-acetaminophen ALF (both in adults and childrens).<sup>[22,23]</sup> The non favourable effect of NAC in indeterminate ALF could be because indeterminate ALF had an advanced grade of encephalopathy (Gr III & IV) and subacute presentation which are related to poor prognosis. In this study age >50 years, III-IV grade of encephalopathy, renal impairment, MELD score > 30 and bilirubin > 20mg/dl were the independent prognostic factors determining mortality.

To the best of our knowledge, the role of NAC in indeterminate ALF has not been studied in prospective controlled trials. The major strengths of this study include prospective cases and controls. Some of the limitations of our study include small sample size, single centre study and the duration of follow up was short (hospital stay till discharge or death in the hospital).

To conclude the overall survival was not improved by NAC in indeterminate ALF. NAC administration did not reduce the duration of hospital stay.

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## REFERENCES

1. Trey C, Davidson CS. The management of fulminant hepatic failure. *Prog Liver Dis* 1970; 3: 282-98.
2. Hoofnagle JH, Carithers RL Jr, Shapiro C, Ascher N. Fulminant hepatic failure: summary of a workshop. *Hepatology* 1995; 21(1): 240-52.
3. Bower WA, Johns M, Margolis HS, Williams IT, Bell BP. Population-based surveillance for acute liver failure. *Am J Gastroenterol* 2007; 102: 2459-63.
4. Rockville. Health Resources and Services Administration, Healthcare Systems Bureau, Division of Transplantation; 2007.
5. Lee WM, Squires Jr RH, Nyberg SL, Doo E, Hoofnagle JH. Acute liver failure: summary of a workshop. *Hepatology*. 2008; 47(4): 1401-15.
6. Bernal W, Wendon J. Acute liver failure. *N Engl J Med* 2013; 369: 2525-34.
7. Ostapowicz G, Fontana R J, Schiodt F V. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. *Ann Intern Med* 2002; 137: 947-54.
8. Lee WM. Etiologies of acute liver failure. *Semin Liver Dis* 2008; 28(2): 142-52.
9. Sugawara K, Nakayama N, Mochida S. Acute liver failure in Japan: definition, classification, and prediction of the outcome. *J Gastroenterol*. 2012; 47(8): 849-61.
10. Acharya SK, Dasarathy S, Kumer TL, Sushma S, Prasanna KS, Tandon A et al. Fulminant hepatitis in tropical population: clinical course, cause, and early predictors of outcome. *Hepatology* 1996; 23: 1448-55.
11. Bernal W. Changing patterns of causation and the use of transplantation in the United Kingdom. *Semin Liver Dis* 2003; 23: 227-37.
12. Wei G, Kalaitzakis E, Bergquist A, Bjornsson E. Long-term follow up of patients with acute liver failure of indeterminate etiology. *Scand J Gastroenterol* 2008; 43: 984-91.
13. Bernal W, Wendon J. Acute liver failure. *N Engl J Med* 2013; 369: 2525-34.
14. Bernal W, Auzinger G, Dhawan A, Wendon J. Acute liver failure. *Lancet* 2010; 376: 190-201.
15. Bernal W, Ma Y, Smith HM, Portmann B, Wendon J, Vergani D. The significance of autoantibodies and immunoglobulins in acute liver failure: a cohort study. *J Hepatol* 2007; 47: 664-70.
16. James LP, Letzig L, Simpson PM, Capparelli E, Roberts DW, Hinson JA, et al. Pharmacokinetics of acetaminophen-protein adducts in adults with acetaminophen overdose and acute liver failure. *Drug Metab Dispos* 2009; 37: 1779-84.
17. Manka P, Bechmann LP, Coombes JD, Thodou V, Schlattjan M, Kahraman A, et al. Hepatitis E virus infection as a possible cause of acute liver failure in europe. *Clin Gastroenterol Hepatol* 2015; 13: 1836-42.
18. Lee WM. Acute liver failure in the United States. *Semin Liver Dis* 2003; 23: 217-26.
19. Schiodt FV, Atillasoy E, Shakil AO, Schiff ER, Caldwell C, Kowdley KV. Etiology and outcome for 295 patients with acute liver failure in the United States. *Liver Transpl Surg* 1999; 5 (1): 29-34.
20. Polson J, Lee WM. American Association for the Study of Liver Disease. AASLD position paper: the management of acute liver failure. *Hepatology* 2005; 41: 1179-97.
21. Nabi T, Nabi S, Rafiq N, Shah A. Role of N-acetylcysteine treatment in non-acetaminophen-induced acute liver failure: A prospective study. *Saudi J Gastroenterol* 2017; 23(3): 169-75.
22. Lee WM, Hynan LS, Rossaro L Fontana RJ, Stravitz RT, Larson AM, et al. Intravenous N-acetylcysteine improves transplant-free survival in early stage non-acetaminophen acute liver failure. *Gastroenterology* 2009; 137: 856-64.
23. Darweesh SK, Ibrahim MF, El-Tahawy MA. Effect of N-Acetylcysteine on mortality and liver transplantation rate in non-

- acetaminophen-induced acute liver failure: a multicenter study. Clin Drug Investig. 2017; 37(5): 473-82.
24. Cotgreave IA. N-acetylcysteine pharmacological considerations and experimental and clinical applications. Adv Pharmacol 1997; 38: 205-27.
  25. Kharazmi A, Nielsen H, Schiotz PO. N-acetylcysteine inhibits human neutrophil and monocyte chemotaxis and oxidative metabolism. Int J Immunopharmacol 1988; 10: 39-46.
  26. Harrison P, Wendon J, Williams R. Evidence of increased guanylate cyclase activation by acetylcysteine in fulminant hepatic failure. Hepatology 1996; 23 (5): 1067-72.
  27. Harrison PM, Wendon JA, Gimson AE, Alexander GJ, Williams R. Improvement by acetylcysteine of hemodynamics and oxygen transport in fulminant hepatic failure. N Engl J Med 1991; 324 (26): 1852-7.
  28. Rank N, Michel C, Haertel C. N-acetylcysteine increases liver blood flow and improves liver function in septic shock patients: results of a prospective, randomized, double-blind study. Crit Care Med 2000; 28: 3799-807.
  29. Bémour C, Vaquero J, Desjardins P, Butterworth RF. N-Acetylcysteine attenuates cerebral complications of non-acetaminophen-induced acute liver failure in mice: antioxidant and anti-inflammatory mechanisms. Metab Brain Dis 2010; 25(2): 241-9.
  30. Lee WM, Larson AM, Stravitz RT. AASLD Position Paper: The Management of Acute Liver Failure: Update 2011. <http://www.aasld.org/practiceguidelines/Documents/AcuteLiverFailureUpdate2011.pdf>. Accessed Jan 2019.
  31. Squires JE, McKiernan P, Squires RH. Acute liver failure: an update. Clinics in liver disease. 2018; 22(4): 773-805.
  32. Nabi T, Rafiq N, Jamil I. Comparative study of Etiological Profile and Outcome in Acute liver failure. Int J Sci Rep 2019; 5(4): 96-102.
  33. Khuroo MS, Kamili S. Aetiology and prognostic factors in acute liver failure in India. J Viral Hepat 2003; 10: 224-31.
  34. European Association for the Study of the Liver. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. J Hepatol. 2017; 66(5):1047-81.

**Table 1: Baseline characteristics of study subjects in the two groups of indeterminate ALF**

Characteristics	NAC group (N = 14)	Control group (N = 16)	P-value*
Categorical variables [n (%)]			
Female gender	8 (57.1%)	9 (56.3%)	0.965
Hepatic- encephalopathy			
Grade I-II	6 (42.8%)	6 (37.5%)	0.305
Grade III-IV	7 (50%)	11 (68.7%)	
Fever	5 (35.7%)	7 (43.7%)	0.661
Vomiting	5 (35.7%)	5 (31.2%)	0.797
Continuous variables [mean ± SD]			
Age (Years)	35.5 ± 16.2	33.9 ± 20.2	0.814
INR	2.2 ± 0.7	2.0 ± 0.9	0.507
Bilirubin (mg/dl)	18.1 ± 8.9	20.8 ± 9.5	0.418
AST (mg/dl)	1014 ± 784	967 ± 512	0.845
ALT (mg/dl)	1110 ± 678	945 ± 589	0.481
Albumin (g/dl)	2.7 ± 0.6	2.9 ± 0.5	0.327
Creatinine (mg/dl)	1.3 ± 0.5	1.4 ± 0.6	0.626
Interval between jaundice and encephalopathy (days)	32 ± 15.8	35 ± 16.2	0.612
Grade of coma	2.4 ± 0.9	2.2 ± 1.1	0.593
MELD Score	31.9 ± 7.9	32.4 ± 5.6	0.841

\*P-value &lt;0.05 is considered statistically significant n = Number; SD = Standard deviation

**Table 2: Length of hospital stay in NAC group and controls in survived patients**

	NAC group	Mean $\pm$ SD (Range)	Control group	Mean $\pm$ SD (Range)	P-value*
Duration of hospital stay of survived patients (days)	9.4 $\pm$ 4.2	(6-15)	11.6 $\pm$ 4.1	(8-16)	0.409

\*P-value <0.05 is considered statistically significant

**Table 3: Survival of study subjects in indeterminate ALF**

	NAC group	n (%)	Control group	n (%)	P-value*
Survival	8 (57.2%)		4 (25%)		0.077

\*P-value <0.05 is considered statistically significant